CLAIMS

What is claimed is:

1. A cross-over protein produced by chemical ligation of two or more functional protein modules derived from two or more different parent protein molecules.

2. The cross-over protein of claim 1, wherein said parent protein molecules are of the same family of protein molecules.

3. The cross-over protein of claim 2, wherein said chemical ligation is selected from the group consisting of native chemical ligation, oxime forming chemical ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, thaizolidine forming ligation, and oxazolidine forming ligation.

4. The cross-over protein of claim 1, wherein said cross-over protein comprises a chemical tag.

5. The cross-over protein of claim 4, wherein said chemical tag is a detectable label.

6. The cross-over protein of claim 5, wherein said detectable label comprises an unnatural amino acid.

7. The cross-over protein of claim 6, wherein said unnatural

amino acid comprises a chromophore.

8. The cross-over protein of claim 7, wherein said chromophore is an acceptor moiety of an acceptor-donor resonance energy transfer pair.

9. The cross-over protein of claim 7, wherein said chromophore is a donor moiety of an acceptor-donor resonance energy transfer pair.

10. The cross-over protein of claim 4, wherein said chemical tag comprises a chemical handle for attaching said cross-over protein to a support matrix.

11. The cross-over protein of claim 10, wherein said cross-over protein is attached to a support matrix via said chemical handle.

12. The cross-over protein of claim 11, wherein said cross-over protein is attached to a support matrix via said chemical handle in a spatially addressable array.

13. The cross-over protein of claim 1, wherein the protein is a cross-over chemokine.

14. The cross-over protein of claim 13, wherein said cross-over chemokine comprises a functional protein module of a chemokine selected from the group consisting of RANTES, SDF1, and MIP.

15. The cross-over protein of claim 14, wherein said functional protein module comprises an N-terminal module corresponding to a SEQ ID NO selected from the group consisting of SEQ ID NO: 9-16.

16. The cross-over protein of claim 14, wherein said functional protein module comprises an C-terminal module corresponding to a SEQ ID NO selected from the group consisting of SEQ ID NO: 17-20.

17. The cross-over protein of claim 14, wherein said cross-over chemokine corresponds to a SEQ ID NO selected from the group consisting of SEQ ID NO: 3, 4, 22-24, 26-39, 41-43 and 45-52.

18. A protein library comprising a collection of cross-over proteins of claim 1.

19. The protein library of claim 18, wherein said collection of cross-over proteins comprises two or more unique cross-over proteins.

20. The protein library of claim 19, wherein one or more of said unique cross-over proteins is produced by chemical ligation of two or more N-terminal peptide segments comprising one or more functional protein modules of a first parent protein and two or more C-terminal peptide segments comprising one or more functional protein modules of a second parent protein.

21. The protein library of claim 18, wherein the cross-over proteins comprise cross-over chemokines.

22. The protein library of claim 21, wherein said cross-over chemokines comprise a functional protein module of a chemokine selected from the group consisting of RANTES, SDF1 and MIP.

23. The protein library of claim 22, wherein said functional protein module comprises an N-terminal module corresponding to a SEQ ID NO selected from the group consisting of SEQ ID NO: 9-16.

24. The protein library of claim 22, wherein said functional protein module comprises an C-terminal module corresponding to a SEQ ID NO selected from the group consisting of SEQ ID NO: 17-20.

25. The protein library of claim 22, wherein one or more of said cross-over chemokines correspond to a SEQ ID NO selected from the group consisting of SEQ ID NO: 3, 4, 22-24, 26-39, 41-43 and 45-52

26. A pharmaceutical composition comprising a cross-over protein according to any one of claims 13-17.

27. A kit comprising a cross-over protein according to any one of claims 1-26.

28. A method of producing a cross-over protein, said method comprising:

ligating under chemoselective chemical ligation conditions (i) at least one N-

terminal peptide segment comprising a functional protein module derived from a first parent protein, and (ii) at least one C-terminal peptide segment comprising a functional protein module derived from a second parent protein having an amino acid sequence that is different from said first parent protein, wherein said N-terminal peptide segment and said C-terminal peptide segment comprise compatible reactive groups capable of chemoselective chemical ligation, whereby a covalent bond is formed between said N-terminal peptide segment and said C-terminal peptide segment so as to produce a chemical ligation product comprising a cross-over protein.

29. The method of claim 28 further comprising the step of repeating said ligating one or more times with one or more second peptide segments selected from the group consisting of an N-terminal peptide segment and a C-terminal peptide segment.

30. The method of claim 28, wherein said parent protein molecules are of the same family of protein molecules.

31. The method of claim 28, wherein said chemoselective chemical ligation is selected from the group consisting of native chemical ligation, oxime forming chemical ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, thaizolidine forming ligation, and oxazolidine forming ligation.

32. A method of producing a cross-over protein library, said method comprising:

ligating under chemoselective reaction conditions a plurality of unique N-terminal peptide segments comprising one or more functional protein modules derived from first parent protein and a plurality of unique C-terminal peptide segments comprising one or more functional protein modules derived from a second parent protein having an amino acid sequence that is different from said first parent protein, wherein said N-terminal peptide segments and said C-terminal peptide segments comprise compatible reactive groups capable of chemoselective chemical ligation, whereby a covalent bond is formed between said N-terminal peptide segments and said C-terminal peptide segments so as to produce a plurality of chemical ligation products comprising a plurality of unique cross-over proteins.

33. The method of claim 32, wherein said plurality of N-terminal peptide segments are obtained by cross-over ligation of two or more different parent protein molecules.

34. The method of claim 32, wherein said plurality of C-terminal peptide segments are obtained by cross-over ligation of two or more different parent protein molecules.

35. The method of claim 32, wherein said parent protein molecules are of the same family of protein molecules.

36. The method of claim 32, wherein said chemoselective chemical ligation is selected from the group consisting of native chemical ligation, oxime forming chemical ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, thiazolidine forming ligation, and oxazolidine forming ligation.

37. A method of screening a cross-over protein library, said method comprising:

contacting a receptor with one or more cross-over proteins obtained from a cross-over protein library, and

identifying a cross-over protein from said library that is a ligand for said receptor in an assay characterized by detection of binding of said ligand to said receptor.

38. The method of claim 37, wherein one or more of said cross-over proteins comprise a detectable label.

39. The method of claim 38, wherein said detectable label comprises a chromophore.

40. The method of claim 38, wherein said detectable label comprises an unnatural amino acid.

41. The method of claim 40, wherein said unnatural amino acid comprises a chromophore.

42. The method of claim 39, wherein said chromophore is an acceptor moiety of an acceptor-donor resonance energy transfer pair.

43. The method of claim 41, wherein said chromophore is a donor moiety of an acceptor-donor resonance energy transfer pair.

44. The method of claim 39, wherein said detection is fluorescence detection.

45. The method of claim 44, wherein said fluorescence detection is fluorescence resonance energy transfer detection.

46. The method of claim 37, wherein said screening is high throughput.

47. The method of claim 37, wherein said cross-over protein library comprises one or more cross-over chemokines.

48. The method of claim 47, wherein said cross-over chemokines comprise a functional protein module of a chemokine selected from the group consisting of RANTES, SDF1, and MIP.

49. The method of claim 48, wherein said functional protein module comprises an N-terminal module corresponding to a SEQ ID NO selected from the group consisting of SEQ ID NO: 9-16.

50. The method of claim 48, wherein said functional protein module comprises an C-terminal module corresponding to a SEQ ID NO selected from the group consisting of SEQ ID NO: 17-20.

51. The method of claim 48, wherein said cross-over chemokine corresponds to a SEQ ID NO selected from the group consisting of SEQ ID NO: 3, 4, 22-24, 26-39, 41-43 and 45-52.